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Perspective

A cross-disciplinary view of current and emerging COVID-19 developments

Catherine M Bennett[a,l], Benjamin Riley[b], Susan Morpeth[c,d], Wen Shi Lee[e,f], Dean A Murphy[g], Krispin Hajkowicz[h,i] and Edwina J Wright[f,j,k] on behalf of the ASHM C19 2023 Conference Organising Committee

[a] Institute for Health Transformation, Deakin University, Melbourne, Victoria, Australia
[b] ASHM Health, formerly known as Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, Sydney, NSW, Australia
[c] Department of Microbiology and Infectious Diseases, Middlemore Hospital, Te Whatu Ora Counties Manukau, Auckland, New Zealand
[d] Faculty of Medical and Health Sciences, University of Auckland, New Zealand
[e] Department of Microbiology and Immunology, University of Melbourne
[f] Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia.
[g] Australian Research Centre in Sex, Health and Society, La Trobe University, Melbourne, Victoria, Australia
[h] Infectious Diseases Unit, Royal Brisbane and Women's Hospital, Queensland, Australia
[i] Centre for Clinical Research, University of Queensland, Brisbane, Australia
[j] Department of Infectious Disease, Alfred Health, Monash University, Melbourne, Victoria, Australia,
[k] The Burnet Institute, Melbourne, Victoria, Australia
[l] Corresponding author: catherine.bennett@deakin.edu.au

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Abstract

The emergency phase of the coronavirus disease 2019 (COVID-19) pandemic is over. Still, the work goes on in understanding the SARS-CoV-2 virus and its evolution, infection impacts – acute and long term – as well as therapeutics and the lessons for preventing and responding to future pandemics. Research into the long-term post-infection effects and therapeutic interventions also expands as the post-infection period lengthens. We provide an overview of the leading edge of COVID-19 research across clinical, epidemiological and social domains.

Key points

- Ongoing challenges in responding to the COVID-19 pandemic include understanding and preventing long COVID, addressing the neurological impacts of SARS-CoV-2 infection, and keeping therapeutics and vaccine development in step with the evolution of the virus

Key points (continued)

- Researchers and policymakers must consider how policy decisions – and political uncertainty – impact how evidence is created and translated during pandemics like COVID-19
- The new Australian Centre for Disease Control faces many challenges but will be vital to the national response to future pandemics

Introduction

More than 3 years in, while there is still much to learn from the coronavirus disease 2019 (COVID-19) pandemic and the causative virus, its evolution and health consequences, we have made extraordinary headway. This paper provides an overview of the outcomes from a meeting of researchers and people with lived experience of COVID-19 infection (Third Australasian COVID-19 Conference [C19 2023]) to share the most recent COVID-19 research findings and reflect on Australia's experience managing the COVID-19 pandemic.†

Unravelling the pathological processes in acute infection and long-term sequelae of long COVID

While considerable uncertainty remains regarding the incidence and persistence of long COVID, especially in children, and there is not yet consensus on a universal case definition, common understandings are emerging. Biomarkers are being explored that will assist diagnosis and management, at least for some, and address uncertainty over prevalence.

Long COVID epidemiology and severity will vary across the globe depending on the degree of infection prevention before vaccines became available. Still, it is believed to have impacted 10% of the more than 650 million COVID-19 cases recorded globally and a proportion of the many more that went unrecorded.[1] More than 200 symptoms associated with long COVID have been identified, with negative impacts across multiple organ systems.[1]

There is a growing understanding of long COVID risk factors. However, we still cannot explain all cases, and it is difficult to distinguish between the pathogenesis of long COVID and potential underlying risk factors, including extant vascular disease, immune dysfunction and microbiome dysbiosis. Immunological aspects of long COVID are also being explored in depth, including whether persistent immune activation and perturbation post-infection are associated with long COVID.[2]

Prevention strategies are also being investigated with emerging evidence for the use of short-course antivirals[3] and the diabetes medication, metformin, which appears to suppress the protein translation of SARS-CoV-2.[4] Vaccinations have been demonstrated to reduce the risk of long COVID and are also being investigated as a potential means of treating long COVID, along with antivirals and anti-inflammatories.[5] What is already clear is that post-viral infection sequelae are not unique to SARS-CoV-2 infection and need to be factored into planning for other viral pandemics.

Neurological sequelae of COVID-19

More than 20% of people experience significant neurological and cognitive symptoms 12 weeks after SARS-CoV-2 infection, and a substantial proportion develop mental health issues.[1] Cognitive impairment is well described with SARS-CoV-2 infection, and impairment rates have been documented to rise to 26% at 12 months post-infection.[6] Possible neuropathogenesis pathways of COVID-19 include neuroinflammation, endothelial dysfunction and upregulation of the kynurenine pathway.[6]

The impact of early SARS-CoV-2 variants on the brain was observed in participants in a biobank study who were infected with the virus early in the pandemic. Following COVID-19 infection, participants' brain scans showed a reduction in grey matter thickness and brain size compared to their pre-pandemic scans.[7] However, the more recent SARS-CoV-2 variants have differing neurovirulence – in mice, the Omicron BA.1 variant is less neurovirulent, but the Omicron BA.5 variant is as neurovirulent as the ancestral strain.[8] These data highlight that we need ongoing research to evaluate the propensity of new SARS-CoV-2 variants to cause neurological damage.

Developments in clinical management and therapeutics

While COVID-19 is now a mild disease for most, it still causes significant morbidity and mortality for immunocompromised people, particularly those with impaired B-cell immunity, people with significant comorbidities and older people. Of note, a recent study found Australian First Nations people had effective immune responses to the COVID-19 BNT162b2 vaccination. However, this response was attenuated in those with comorbidities.[9] Health systems continue to struggle with the burden of surges of COVID-19 infection in the population and managing infection control in healthcare settings.

The benefit of using antiviral agents in the community remains uncertain, with limited real-world data and analyses complicated by the biases introduced by antiviral administration guidelines. Antivirals, including nirmatrelvir-ritonavir and molnupiravir were associated with reduced COVID-19 hospitalisations and deaths in a large observational cohort study in Hong Kong.[10] Similar findings have also been reported against a backdrop of more recent SARS-CoV-2 variants (BA.4/5) in a highly vaccinated population aged over 70 years in Victoria, Australia.[11] However, the protection conferred by monoclonal antibodies for individuals in high-risk groups has been disappointingly short-lived as new variants emerge. Virus-specific T-cell immunotherapy may represent a new hope for immunocompromised people with persistent symptomatic disease.[12,13]

COVID-19 is a prothrombotic disease. Therapeutic anticoagulation provides no survival benefit in critically ill patients with COVID-19 compared to a standard prophylactic dose. However, it may be associated with increased survival in hospitalised people not requiring critical care.[14,15] Intermediate dose anticoagulation warrants further exploration.[16] The success of immune modulation with corticosteroids, interleukin-6 receptor blockers (tocilizumab) and Janus kinase (JAK) inhibitors (baricitinib) for patients with COVID-19 pneumonitis has been notable.[17] This holds promise for other respiratory infections, such as community-acquired pneumonia and influenza.

The rapid development of effective mRNA vaccines is one of the great technological successes of the pandemic. Small interfering RNA (siRNA) delivered to respiratory mucosal cells using innovative lipid nanoparticle formulation also shows promise for development as prophylaxis[13] and a novel class of antiviral therapeutics.[18] Australia's first mRNA vaccine manufacturing facility is expected to be operational in 2024 in Melbourne, Victoria, representing a partnership between the Australian Federal and Victorian Governments, Monash University and pharmaceutical company Moderna.

Bridging science, politics, policy and the public in a pandemic

Uncertainty will always be part of pandemics. In a panel discussion at the C19 2023 conference, virologists Yong-Zhen Zhang and Eddie Holmes, who together released the SARS-CoV-2 genome 11 days after the Wuhan outbreak, observed that while national and international data sharing is central and critical, it is also informed by uncertain political contexts.[19]

Given how evidence is rapidly produced, transformed and communicated, researchers and policymakers must consider how evidence, like modelling, creates and is created by policy decisions.[20] For example, while the global COVAX initiative to ensure equitable access to vaccines (co-led by Coalition for Epidemic Preparedness Innovations, Gavi – the Vaccine Alliance and the World Health Organization [WHO]) has had some success in negotiating vaccine supply, we must stay focused on the adage '*vaccines don't save lives, vaccinations do*'.[21]

How outbreak responses have been designed and executed is also deeply entangled in the political and social worlds.[22] Aged care, immigration detention and public housing towers have been highlighted as some of the settings where carceral logics predominated, and policy measures constructed marginalised people as both 'vulnerable' and as public health threats. Such constructions create stigma and undermine public engagement, which is an essential element of successful disease control at the population level. Recently, O'Donnell et al. reported the sobering findings that COVID-19 infections were 2.9 to 5.6 times higher in the most ethnically diverse council areas in Melbourne and Sydney, respectively, and that excess deaths were nearly 30% higher in diverse communities between 2020–2021.[23]

The role of the new Australian Centre for Disease Control (ACDC)

Australia was the only OECD country to enter the pandemic without a national-level disease control entity. This was particularly challenging given the federated nature of the public health systems and pandemic response. Australia's current Chief Medical Officer, Professor Paul Kelly, will be the incoming interim Director of the new Australian Centre for Disease Control (ACDC) to be established in 2024 and has highlighted the breadth of its remit within fundamental public health principles, including proportionality of response, balancing autonomy and social benefits, equity and transparency in decision making.[24]

The ACDC aims to put Australia on the front foot in the face of future pandemics, informed by real-time information integrated with national security and

international intelligence. The ACDC will provide the vehicle for rapid advice from experts to the government. The design and function of the ACDC will draw from all we have learned and are still learning from COVID-19.

Technological developments have placed Australia in a better position for national coordination in pandemic preparedness. However, global politics will inform responses, making international relations critical for the ACDC. Leadership in coordinated real-world data collection and analysis will enable more nuanced approaches to pandemic monitoring and response. This requires seamless data linkage – which is only now emerging in Australia. The ACDC can provide nationally coordinated support to state and federal public health workforces. It can help ensure infrastructure is in place for the initial pandemic response and major public health programs, such as urgent vaccine rollouts at scale. But underpinning all of this, Australia needs to establish the surge infrastructure (laboratory capacity, workforce and expertise, IT) and ensure that the valuable corporate knowledge built during the pandemic is not lost.

There will be challenges – the new ACDC has to balance a broad set of priorities and operate as a national body within a federated public health system. But if Australia could achieve what it did during the pandemic with its extant planning and infrastructure, punching above its weight globally, imagine what will be possible with the lessons learned, infrastructure investment and the ACDC in place.

Virologists Yong-Zhen Zhang and Eddie Holmes, together with Dominique Dwyer (a member of the WHO team that investigated the virus's origins), remind us that the early reporting of a new human pathogen is to be encouraged, not feared.[19] Open, nonpartisan and ongoing information sharing is vital to identifying and responding to future pandemics.

†Footnote

This paper draws on the third Australasian COVID-19 Conference (C19 2023) (see: https://covid-19conference.com.au/), which was held by ASHM Health, formerly known as Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), in Brisbane, Queensland, on 27–28 July 2023. The conference collated the current state of knowledge of basic research, social science, clinical research and epidemiology, providing a unique cross-disciplinary status overview and input from those with lived experience to share what we have learned so we can plan for the future. This paper captures the essence of the meeting. It outlines recurring themes that need ongoing attention: building evidence, challenging uncertainty, and remaining alert to changes in COVID-19 medicine and politics.

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Peer review and provenance

Internally peer reviewed, invited.

Competing interests

CB declares honorarium from Novavax as part of the Australian Vaccine Advisory Group; acting as an expert witness on a range of legal cases relating to the pandemic and other epidemiological matters; and payment from Moderna for presenting on COVID-19 issues. BR is employed by the ASHM, which convened the Australasian COVID-19 Conference 2023. SM reports a grant from the Health Research Council of New Zealand for participation in ASCOT and REMAP-CAP trials for COVID-19 treatment; was a member of the Therapeutics Advisory Group to the New Zealand Ministry of Health and a member of the NZ national guidelines writing group for COVID-19. KH reports a grant and consulting fees/honorarium from Gilead Sciences and consulting fees and travel support from Moderna to attend meetings.

Author contributions

CB and EW drafted the paper summarising key points of the C19 2023 conference, and all authors contributed to final text and provision of the most relevant publications to cite within their areas of expertise.

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